DRUG RELEASING BIODEGRADABLE FIBER IMPLANT

The present invention claims priority to provisional application serial No. 60/147,827, filed Aug. 6, 1999.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to the field of medicine and tissue engineering, and in particular to drug releasing biodegradable implants.

2. Description of Related Art

Tissue engineering is a discipline wherein living cells are used to replace functional loss because of injury, disease, or birth defect in an animal or human. These replacement cells can be autologous, allogenic, or, in limited circumstances, xenogenic. The field of tissue engineering is a new area of medicine and optimal procedures have yet to be elucidated.

At present, there are several primary avenues investigators are using to engineer tissues. One is to harvest cells from a healthy donor, preferably from the same individual, or at least from an appropriate donor of the same species, and grow those cells on a scaffold in vitro. This scaffold is typically a three-dimensional polymer network, often composed of biodegradable fibers. Cells adherent to the polymer network can then typically be induced to multiply. This cell filled scaffold can be implanted into the impaired host with the goal that the cells will perform their physiological function and avoid destruction by the host immune system. To this end, it is important that purified cell lines are used, as the introduction of non-self immune cells can up-regulate a strong host immune attack. The difficulty with this approach is the scaffolding must be small, as no cell can survive more than a couple millimeters away from a source of oxygen and nutrients. Therefore, large scaffolds cannot be used, as the scaffold will not vascularize adequately in time to save the cells in the interior regions.

In another approach, an empty three-dimensional, biodegradable polymer scaffold is directly implanted in the patient, with the goal of inducing the correct type of cells from the host's body to migrate into the polymer scaffold. The benefit is that vascularization can happen simultaneously with migration of cells into the matrix. A major problem is that there is currently no way to ensure that the appropriate cell types will migrate into the scaffold, and that the mechanical and biological properties will be maintained to provide the patient's physiological need.

In both of the above approaches, the scaffold may be biodegradable, meaning that over time it will break down both chemically and mechanically. As this break down occurs, the cells secrete their own extracellular matrix, which plays a critical role in cell survival and function. In normal tissue, there is an active and dynamic reciprocal exchange between the constitutive cells of the tissue and the surrounding extracellular matrix. The extracellular matrix provides chemical signals that regulate the morphological properties and phenotypic traits of cells and may induce division, differentiation or even cell death. In addition, the cells are also constantly rearranging the extracellular matrix. Cells both degrade and rebuild the extracellular matrix and secrete chemicals into the matrix to be used later by themselves or other cells that may migrate into the area. It has also been discovered that the extracellular matrix is one of the most important components in embryological development. Pioneering cells secrete chemical signals that help following cells differentiate into the appropriate final phenotype. For example, such chemical signals cause the differentiation of neural crest cells into axons, smooth muscle cells or neurons.

The integrated relationship between extracellular matrix and tissue cells establishes the extracellular matrix as an important parameter in tissue engineering. If cells are desired to behave in a specific manner, then the extracellular matrix must provide the appropriate environment and appropriate chemical/biological signals to induce that behavior for that cell type. Currently it is not possible to faithfully reproducer a biologically active extracellular matrix. Consequently, some investigators use a biodegradable matrix that enables the cells to create their own extracellular matrix as the exogenous matrix degrades.

In the above-described approaches to tissue engineering, a polymer scaffolding provides not only the mechanical support, but also the three-dimensional shape that is desired for the new tissue or organ. Because cells must be close to a source of oxygen and nutrients in order to survive and function, a major current limitation is that of blood supply. Most current methodologies provide no specific means of actively assisting the incorporation of blood vessels into and throughout the polymer matrix. This places limitations on the physical size and shape of the polymer matrix. The only current tissue-engineering device that has made it into widespread clinical use is artificial skin, which by definition is of limited thickness. The present invention provides compositions and methods that promote the directed migration of appropriate cell types into the engineered extracellular matrix. By directing specific three-dimensional cell migration and functional patterns, directed vascularization can be induced, which overcomes the current limitations on the shape and size of polymer implants. It also ensures that appropriate cell types will be physically located in specific locations within the matrix. Compositions and methods are provided to modulate phenotypic expression as a function of both time and space.

SUMMARY OF THE INVENTION

The present invention provides tissue engineering compositions and methods wherein three-dimensional matrices for growing cells are prepared for in vitro and in vivo use. The matrices comprise biodegradable polymer fibers capable of the controlled delivery of therapeutic agents. The spatial and temporal distribution of released therapeutic agents is controlled by the use of predefined nonhomogeneous patterns of polymer fibers, which are capable of releasing one or more therapeutic agents as a function of time. The terms "scaffold," "scaffold matrix" and "fiber-scaffold" are also used herein to describe the three dimensional matrices of the invention. "Defined nonhomogeneous pattern" in the context of the current application means the incorporation of specific fibers into a scaffold matrix such that a desired three-dimensional distribution of one or more therapeutic agents within the scaffold matrix is achieved. The distribution of therapeutic agents within the matrix fibers controls the subsequent spatial distribution within the interstitial medium of the matrix following release of the agents from the polymer fibers. In this way, the spatial contours of desired concentration gradients can be created within the three dimensional matrix structure and in the immediate surroundings of the matrix. Temporal distribution is controlled by the polymer composition of the fiber and by the use of coaxial layers within a fiber.

One aspect of the present invention is a biocompatible implant composition comprising a scaffold of biodegradable